IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

BOARD OF PATENT APPEALS AND INTERFERENCES

In re application of:

Thomas M. BEHR and David M. GOLDENBERG — Group Art Unit: 1642

Serial No.: 09/200,791 — Examiner: L.R. Helms

Filing Date: November 30, 1998

For: METHODS FOR REDUCED RENAL UPTAKE OF PROTEIN CONJUGATES

BRIEF ON APPEAL

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Attorney Docket No. 018734/0161

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APPELLANT'S BRIEF UNDER 37 CFR §1.192

Commissioner of Patents
Washington, D.C.

Sir:

This brief is in furtherance of the Notice of Appeal filed in this case on February 14, 2003. The period for response has been extended to expire on June 14, 2003, by virtue of the petition and fee, in the amount of $205.00, Check No. 28887, as filed in the U.S. Patent and Trademark Office on May 15, 2003. The fees for the Appeal Brief required under 37 CFR §1.17(c) are included in our accompanying Check No. 29406. Please charge any fee deficiency or credit any overpayment to Deposit Account 19-0741.

This brief is transmitted in triplicate in conformance with 37 CFR §1.192(a).

I. REAL PARTIES IN INTEREST

The real party in interest in this case is Center for Molecular Medicine and Immunology.

II. RELATED APPEALS AND INTERFERENCES

There are no appeals or interferences that are directly related to the present case.

III. STATUS OF CLAIMS

Pending claims: 1-9, 11-21, 23-29 and 31-37

Rejected claims: 1-9, 11-21, 23-29 and 31-37

Appealed claims: 1-9, 11-21, 23-29 and 31-37

A copy of Appellants' pending claims is attached hereto as APPENDIX A.

IV. STATUS OF AMENDMENTS

No claim amendments were made following final rejection, and all claim amendments have been entered into the record. In Applicants' amendment dated February 14, 2003, Applicants attempted to add new claim 38. However, in the Advisory Action dated March 3, 2003, the Examiner stated that new claim 38 raised issues that would require further consideration and/or search.

V. BACKGROUND AND SUMMARY OF THE INVENTION

The present invention relates to a method of reducing kidney retention of a protein conjugate in a patient. The relatively high uptake and retention of radioactivity in the kidneys represents a major drawback to the use of protein conjugates comprising a radiolabel for imaging and therapy. Renal uptake of peptides and small protein is thought to occur via glomerular filtration of molecules smaller than 60 kD, with subsequent tubular reabsorption for lysosomal degradation. When radioisotopes such as iodine are liberated by this degradative process they are released quickly from the cell, but radiometals are retained by binding to ubiquitous intracellular proteins with high affinity for metal ions[1]. The present invention provides a convenient method for reducing renal retention of radiolabeled proteins and protein conjugates of cytotoxic agents.

The inventive method for reducing kidney retention of a protein conjugate involves administering to a patient a protein conjugate and one or more compounds selected from D-lysine, poly-lysine having a molecular weight in the range of 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof. The protein conjugate is not an antibody or an antibody fragment and has a molecular weight that does not

[1] Specification page 2, lines 13-19; U.S. Patent No. 5,843,894, column 1, lines 32-38.

exceed 60 kD. The pharmaceutically acceptable salt and carboxyl derivative of poly-lysine has a molecular weight in the range of 1-60 kD.

VI. ISSUES

There is one issue stated in the Final Rejection. This issue, which is on appeal, is the propriety of a rejection of claims 1-9, 11-21, 23-29, and 31-37 under 35 U.S.C. § 103 as allegedly being unpatentable over Behr et al. (Cancer Research 55:3825-3834, September 1, 1995), and further in view of Grey et al. (U.S. Patent No. 5,380,513) and Raines et al. (U.S. Patent No. 5,840,296).

VII. GROUPING OF CLAIMS

For purposes of this appeal, all of the claims stand or fall together.

VIII. SUMMARY OF THE ARGUMENTS

The Examiner's rejection of claims 1-9, 11-21, 23-29, and 31-37 under 35 U.S.C. §103 for allegedly being unpatentable over Behr et al. in view of Grey et al. and Raines et al. is based on Behr et al.'s alleged teaching of a method of reducing renal uptake in a patient of a protein conjugate comprising an imaging or therapeutic moiety involving the addition of lysine and poly-lysine. The Examiner acknowledges that Behr et al. fails to teach a protein conjugate that is not an antibody conjugate or a conjugate comprising a ribonuclease. However, the Examiner asserts that Grey et al. and Raines et al. cure the deficiencies of Behr et al. because Grey et al. teach a method to reduce renal retention of protein conjugates with lysine and Raines et al. teach conjugates comprising ribonuclease which have been effective in tumor patients and that the decrease in renal function of Onconase may be the consequence of an inability to effectively clear the Onconase protein from the kidneys.

In contrast to the Examiner's rejection, the present invention is patentable over Behr et al. in view of Grey et al. and Raines et al. Behr et al. and Raines et al. are not prior art against the present application because the present application is entitled to a priority date of March 21, 1995.

IX. ARGUMENTS

Behr Et Al. And Raines Et Al. Are Not Prior Art Against The Present Application

The present application is a continuation-in-part application of U.S. Application No. 08/407,899 (hereafter "the '899 application), filed March 21, 1995. Because the present claims are supported by the disclosure of the '899 application, and because Behr et al. was published after March 21, 1995[2] and Raines et al. was filed after March 21, 1995[3], Behr et al. and Raines et al. are not valid prior art against the present application.

In the Office Action dated January 28, 2002 (paper No. 20), the Examiner asserted that a method of reducing kidney retention of a protein conjugate that is not an antibody or an antibody fragment conjugate is not supported by the '899 application. In the Advisory Action dated March 3, 2003 (paper No. 26), the Examiner asserted that there is no support for excluding antibodies or fragments of antibodies in the '899 application. Applicants respectfully disagree with the Examiner and assert that the present claims are entitled to the priority date of the '899 application.

Applicants do not dispute that the instant application is a CIP and that expanded examples and description were added to the instant specification. However, the mere fact that a specification contains new matter does not mean that a given claim is not entitled to an earlier prior date. To the contrary, each claim must be examined individually to determine whether the parent '899 application contains support for the claims in question. In the instant application, the claims are supported. There are no claims pending that are directed to the specific embodiments constituting the new matter that was added in the CIP.

In particular, on page 2, lines 1-8 of the '899 application (column 1, lines 33-39 of the issued patent), a description of a potential mechanism for renal uptake of peptides and small proteins is provided. This passage evidences that the specification is directed broadly to a method for reducing renal uptake of peptide and small protein conjugates (whether antibody or non-antibody), and those methods are exemplified with antibody or antibody fragment conjugates. One of ordinary skill in the art, reading the specification as a

[2] Behr et al. was published on September 1, 1995.

[3] Raines et al. was filed on October 15, 1997.

whole, would readily understand that Applicants possessed a generic scope extending to all such cytotoxic or imaging agents that are susceptible to renal uptake. Coupling the specification's explicit reference to "cytotoxic or imaging agents" with the explanation of the mechanism and the explicit reference to peptides and small proteins, there is at least implicit support in the '899 application for the presently claimed invention and no basis to deny these claims their rightful priority date.

Verbatim support has never been required. The courts have held that a broadening omission of an element is permitted where the specification as a whole suggests it is not necessary to the operation of the invention. Compare In re Peters, 723 F.2d 891, 221 USPQ 952 (Fed. Cir. 1983) (In a reissue application, a claim to a display device was broadened by removing the limitations directed to the specific tapered shape of the tips without violating the written description requirement. The shape limitation was considered to be unnecessary since the specification, as filed, did not describe the tapered shape as essential or critical to the operation or patentability of the claim.). "[T]he specification *as a whole* must be considered in determining whether the scope of enablement provided by the specification is commensurate with the scope of the claims." In re Johnson, 194 USPQ 187, 195 (CCPA 1977), citing In re Moore, 169 USPQ 236, 238-239 (CCPA 1971) (emphasis in original).

The '899 application does not indicate that it is critical or essential that the conjugate is an antibody or antibody fragment conjugate, and in describing the background, clearly indicates the applicability of the mechanism to non-antibody targeting proteins/peptides as well as antibody fragments. The mechanism described in the '899 application is reducing renal uptake by administering an effective amount of one or more compounds selected from the group consisting of D-lysine, poly-D-lysine, and poly-L-lysine, or a pharmaceutically acceptable salt or carboxyl derivative thereof. Therefore, the '899 application supports a method for reducing kidney uptake of protein conjugate that is not an antibody or an antibody fragment.

The '899 application contains support for a method of reducing kidney retention of a protein conjugate that is not an antibody or an antibody fragment conjugate. A method for reducing kidney uptake of an antibody or an antibody fragment conjugate is an embodiment of the invention disclosed in the '899 application. An antibody is a *protein* that is structured to react with a specific antigen. *See* Online Biology Dictionary definition of

"antibody" (attached). Thus, antibodies are a species of the protein genus. On page 2, lines 1-8 of the '899 application, a description of a potential mechanism for renal uptake of peptides and small proteins is provided. This passage evidences that the specification is directed broadly to a method for reducing renal uptake of peptide and small protein conjugates, and those methods are exemplified with antibody or antibody fragment conjugates.

The court has held that "[d]escriptions of species amounting in the aggregate to the same thing [as a generic description]" provide adequate support under 35 U.S.C. § 112, paragraph 1. In re Johnson, 194 USPQ 187, 196 (CCPA 1977), quoting In re Welstead, 174 USPQ 449 (CCPA 1972).[4] The '899 application, including the examples, background and summary sections, describes a method for reducing kidney uptake of antibody and antibody fragment conjugates.

Because the claims are entitled to the parent filing date, Behr et al. and Raines et al. are not prior art against the present application.

X. CONCLUSION

For the above reasons, the Board is respectfully requested to reverse the Examiner and remand this application for allowance.

Respectfully submitted,

June 13, 2003
Date

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[4] In In re Johnson, Appellants were prosecuting a continuation-in-part application in which the claims recited a proviso excluding two species specifically disclosed in the parent application. In order to overcome a prior art rejection, Appellants attempted to rely on the priority date of a parent application. However, the Examiner stated that the parent application did not contain support for the "limited genus" created by the proviso. The court reversed the rejection, holding that the parent disclosure satisfied § 112, first paragraph, for the 'limited genus' claimed after exclusion from the original claims of two species specifically disclosed in the parent application. *See* In re Johnson, 194 USPQ 187, 195 (CCPA 1977).

APPENDIX A: APPEALED CLAIMS

1. A method of reducing kidney retention of a protein conjugate in a patient, comprising administering to said patient one or more compounds selected from the group consisting of D-lysine, poly-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof, wherein said protein conjugate has a molecular weight that is not greater than about 60 kD and is not an antibody or antibody fragment conjugate,

wherein the pharmaceutically acceptable salt and carboxyl derivative of poly-lysine has a molecular weight in the range 1-60 kD,

whereby said compound or compounds reduce kidney retention of said conjugates.

2. A method according to claim 1, wherein said protein conjugate is selected from the group consisting of protein conjugates, peptide conjugates, polypeptide conjugates, glycoprotein conjugates and lipoprotein conjugates.

3. A method according to claim 1, wherein said protein conjugate is a radiolabeled conjugate.

4. A method according to claim 3, wherein the radiolabel in said radiolabeled conjugate is an imaging isotope.

5. A method according to claim 3, wherein the radiolabel in said radiolabeled conjugate is an therapeutic isotope.

6. A method according to claim 1, wherein said protein conjugate is selected from the group consisting of radiolabeled hapten conjugates and haptens conjugated to a cytotoxic agent.

7. A method according to claim 1, wherein said protein conjugate comprises a cytotoxic agent.

8. The method according to claim 1, wherein D-lysine is administered to said patient.

9. The method according to claim 1, wherein poly-D-lysine is administered to said patient.

11. The method according to claim 1, wherein a mixture of at least two of said compounds is administered to said patient.

12. The method according to claim 1, wherein said poly-lysine has a molecular weight of 15-30 kD.

13. The method according to claim 1, wherein said compound is parenterally administered to said patient in a physiologically acceptable aqueous solution.

14. The method according to claim 13, wherein said physiologically acceptable aqueous solution is administered to said patient by continuous infusion.

15. The method according to claim 13, wherein said physiologically acceptable aqueous solution is administered to said patient by means of at least one injection of a bolus of said solution.

16. The method according to claim 15, wherein said physiologically acceptable aqueous solution is administered to said patient by means of at least one injection of a bolus of said solution followed by oral administration in a physiologically acceptable carrier

17. The method according to claim 1, wherein said compound is orally administered to said patient in a physiologically acceptable carrier.

18. A method of reducing kidney retention of a protein conjugate in a patient undergoing treatment with a targeting protein conjugate comprising administering to said patient, one or more compounds selected from the group consisting of D-lysine, poly-lysine having a molecular weight in the range 1-60 kD, pharmaceutically acceptable salts thereof and carboxyl derivatives thereof, wherein said protein conjugate has a molecular

weight that is not greater than about 60 kD and is not an antibody or antibody fragment conjugate,

wherein the pharmaceutically acceptable salt and carboxyl derivative of poly-lysine has a molecular weight in the range 1-60 kD,

whereby said compound or compounds reduce kidney retention of said conjugates.

19. A method according to claim 18, wherein said protein conjugate is selected from the group consisting of protein conjugates, peptide conjugates, polypeptide conjugates, glycoprotein conjugates, and lipoprotein conjugates.

20. A method according to claim 18, wherein said targeting protein conjugate comprises a ribonucleic acid binding protein.

21. A method according to claim 20, wherein said ribonucleic acid binding protein is a ribonuclease.

23. A method according to claim 18, wherein said protein conjugate is a radiolabeled conjugate.

24. A method according to claim 23, wherein the radiolabel in said radiolabeled conjugates is an imaging isotope.

25. A method according to claim 23, wherein the radiolabel in said radiolabeled conjugates is a therapeutic isotope.

26. A method according to claim 18, wherein said protein conjugate is selected from the group consisting of radiolabeled hapten conjugates and haptens conjugated to a cytotoxic agent.

27. A method according to claim 18, wherein said protein conjugate comprises a cytotoxic agent.

28. The method according to claim 18, wherein D-lysine is administered to said patient.

29. The method according to claim 18, wherein poly-D-lysine is administered to said patient.

31. The method according to claim 18, wherein a mixture of at least two of said compounds is administered to said patient.

32. The method according to claim 18, wherein said poly- lysine has a molecular weight of 15-30 kD.

33. The method according to claim 18, wherein said compound is parenterally administered to said patient in a physiologically acceptable aqueous solution.

34. The method according to claim 33, wherein said physiologically acceptable aqueous solution is administered to said patient by continuous infusion.

35. The method according to claim 34, wherein said physiologically acceptable aqueous solution is administered to said patient by means of at least one injection of a bolus of said solution.

36. The method according to claim 35, wherein said physiologically acceptable aqueous solution is administered to said patient by means of at least one injection of a bolus of said solution followed by oral administration in a physiologically acceptable carrier .

37. The method according to claim 18, wherein said compound is orally administered to said patient in a physiologically acceptable carrier.

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